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REVIEW

Microbiome and gut-liver interactions: From mechanisms to therapies

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Abstract

The gut-liver axis represents a bidirectional and dynamic communication system between the gastrointestinal tract and liver, critically modulated by gut microbiota, bile acids, immune responses, and metabolic pathways. Disruption of this finely tuned axis contributes to the pathogenesis of several liver diseases, including alcohol-associated hepatitis, metabolic dysfunction-associated steatotic liver disease, cirrhosis, hepatic encephalopathy, and cholangiopathies like primary biliary cholangitis and primary sclerosing cholangitis. Dysbiosis, marked by reduced microbial diversity and dominance of pathogenic species, alters bile acid metabolism, increases gut permeability, and fuels hepatic inflammation. In cholangiopathies, the gut microbiome modulates immune dysregulation and fibrosis through complex microbial-host interactions. Emerging therapies targeting the microbiota, such as fecal microbiota transplantation, antibiotics (*e.g.*, rifaximin, vancomycin), bile acid modulators, and probiotics, show promise in restoring microbial equilibrium, improving liver biochemistry, and reducing disease progression. Precision medicine strategies integrating genomics, metabolomics, and microbiomics offer a tailored approach for therapy and prognosis. This review highlights the central role of the gut-liver axis in liver diseases and the potential of microbiome-based interventions to shift management from symptomatic relief toward disease modification and personalized hepatology, underscoring a new frontier in liver disease therapeutics.

Key Words: Microbiome; Hepatic encephalopathy; Steatotic liver disease; Fecal microbiota transplantation; Cholangiopathies

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Core Tip: The gut-liver axis is emerging as a key player in chronic liver disease pathogenesis and treatment. From alcoholic hepatitis to cholangiopathies like primary biliary cholangitis and primary sclerosing cholangitis, disruptions in the gut microbiota fuel liver inflammation, fibrosis, and immune dysregulation. This review explores how targeting the microbiome through fecal microbiota transplantation, bile acid modulators, and precision medicine can transform liver disease management. With growing evidence supporting microbiome-based interventions, this article offers a compelling look into how restoring gut-liver harmony may shift treatment from symptom control to disease reversal, unlocking the future of personalized hepatology.

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INTRODUCTION

The gut-liver axis reflects the complex and interdependent relationship between the gastrointestinal tract, including its microbiota, and the liver, modulated by metabolic, immunologic, and neuroendocrine signals[1]. As the liver receives nutrient-rich blood *via* the portal vein, it is also exposed to translocated microbes and their associated metabolites and components. In return, the liver secretes bile acids, immunoglobulins, and other factors that shape the intestinal microbiome and preserve mucosal barrier function. This interplay also maintains immune tolerance and homeostasis; however, in chronic liver diseases, disruption of this balance can promote hepatic injury and inflammation[2,3].

Under normal physiological conditions, a well-structured and functional intestinal barrier comprised of multiple defensive layers effectively limits microbial exposure by preventing excessive translocation and maintaining host-microbiota segregation. Alterations in gut microbial composition, commonly referred to as microbiome dysbiosis, have been increasingly associated with a broad spectrum of liver disorders, including alcohol-associated hepatitis (AH), metabolic dysfunction-associated steatotic liver disease (MASLD), cirrhosis, hepatic encephalopathy (HE), primary biliary cholangitis (PBC), and primary sclerosing cholangitis (PSC)[4]. Gut microbiome dysbiosis is characterized by reduced microbial diversity, enrichment of pro-inflammatory pathobionts (*e.g.*, *Veillonella*, *Enterococcus*, *Klebsiella*), and depletion of beneficial commensals like *Faecalibacterium prausnitzii* and *Bacteroides thetaiotaomicron*, which play critical roles in maintaining intestinal and hepatic homeostasis[5-7].

Emerging evidence supports a central role of the microbiota in disease pathogenesis and progression. In PSC and PBC, microbial dysbiosis has been linked to increased intestinal permeability, immune dysregulation, altered bile acid metabolism, and hepatic fibrosis[7-10]. Similarly, in HE, altered gut microbial composition contributes to hyperammonemia, endotoxemia, systemic inflammation, and neuroinflammation[11,12]. In cirrhosis, intestinal dysmotility with delayed small intestinal transit time contributes to the development of small intestinal bacterial overgrowth (SIBO). This leads to bacterial translocation into the systemic circulation, further exacerbating dysbiosis and increasing the risk of HE [13]. Pande *et al*[14] showed that SIBO incidence increases as cirrhosis worsens, with 20% found in Child-Pugh class A compared with 73% in Child-Pugh class C. Figure 1 provides a summary of the mechanisms through which gut microbiome dysbiosis causes various hepatic pathologies.

Therapeutic strategies targeting the gut-liver axis are gaining momentum. Fecal microbiota transplantation (FMT) has demonstrated encouraging results in PBC, PSC, and HE, with improvements in alkaline phosphatase (ALP) levels, bacterial diversity, and neurocognitive function[15,16]. Rifaximin alters microbial metabolism and endotoxin production, improving cognition and reducing oxidative stress without significant shifts in bacterial taxa[12,17]. Novel approaches such as bacteriophage therapy and genetically engineered microbial strains (*e.g.*, SYNB1020) offer additional tools to correct microbial imbalance and modulate host-microbe interactions[9-11].

In parallel, advances in multi-omics and precision medicine allow for individualized therapeutic approaches. Integration of genomics, metabolomics, and microbiomics enables patient stratification based on microbial risk signatures and response predictors[18,19]. For example, Mendelian randomization studies have identified specific microbial taxa causally linked to PBC[20], while microbiota-enhanced scoring systems improve the prognostic accuracy of the model for end-stage liver disease score in cirrhosis[21,22].

This review explores the role of the gut-liver axis in liver disease pathogenesis and highlights emerging microbiome-targeted therapies. Special emphasis is placed on their implications in PSC, PBC, HE, AH, and MASLD, with a focus on FMT, antibiotics, bile acid modulators, and precision strategies. As our understanding of the microbiome-immune-metabolic interface expands, targeting the gut-liver axis offers a promising path from symptomatic control toward disease modification and precision hepatology.

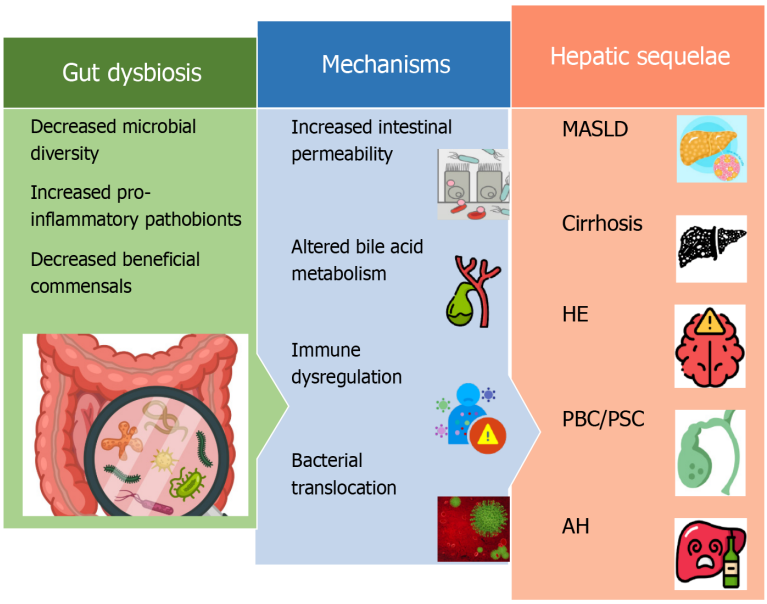

Figure 1 Gut dysbiosis-driven mechanisms contributing to hepatic sequelae. Disruption of the gut microbiota (dysbiosis) is characterized by decreased microbial diversity, loss of beneficial commensals, and expansion of pro-inflammatory pathobionts. This dysbiosis contributes to liver disease through increased intestinal permeability, altered bile acid metabolism, immune dysregulation, and bacterial translocation. These pathophysiological mechanisms are implicated in the development and progression of various liver conditions, including metabolic dysfunction-associated steatotic liver disease, cirrhosis, hepatic encephalopathy, primary biliary cholangitis, primary sclerosing cholangitis, and alcoholic hepatitis. MASLD: Metabolic dysfunction-associated steatotic liver disease; HE: Hepatic encephalopathy; PBC: Primary biliary cholangitis; PSC: Primary sclerosing cholangitis; AH: Alcoholic hepatitis.

METHODOLOGY

This narrative review aimed to summarize the current understanding of the gut microbiome and its interaction with the liver, particularly through the gut-liver axis. A comprehensive search of the PubMed database was conducted to identify relevant peer-reviewed articles published in English between 1984 and 2025. Search terms included combinations of keywords and MeSH terms such as "gut microbiome", "gut-liver axis", "dysbiosis", "cirrhosis", "hepatic encephalopathy", "bile acids", "short-chain fatty acids", "primary sclerosing cholangitis", "primary biliary cholangitis", "fecal microbiota transplant (FMT)", and "microbiome modulation", using Boolean operators (AND, OR).

Study selection

Initially, a total of 420 articles were retrieved. After screening, 235 articles were excluded based on the following exclusion criteria: (1) Non-English language publications; (2) Irrelevant focus (*i.e.*, not addressing the gut-liver axis); and (3) Articles lacking significant pathophysiological or clinical relevance. This resulted in 185 articles that were screened in detail, from which 85 studies were included in the final review (Figure 2).

Inclusion criteria

Original research (prospective/retrospective cohort studies), meta-analyses and systematic reviews, clinically significant case reports, basic and translational research exploring the gut-liver axis, and studies discussing microbiome modulation (*e.g.*, FMT, probiotics). Reference lists of selected publications were also manually screened to capture additional relevant studies. No formal quality or risk-of-bias assessment was conducted due to the descriptive and narrative nature of this review. While every effort was made to include significant literature, some relevant articles may have been inadvertently omitted.

WHAT IS THE GUT-LIVER AXIS?

The portal vein serves as a key anatomical conduit that facilitates communication between the gut and the liver. It transports microbial metabolites, dietary components, and other gut-derived substances directly to the liver. In return, the liver regulates intestinal function and microbial composition through the secretion of bile acids and immunoglobulins, creating a dynamic feedback loop that maintains gut-liver homeostasis[1].

It is crucial to understand that intestinal epithelial barrier integrity plays a key role in maintaining gut-liver homeostasis. One of the primary elements is the protective mucus layer secreted by the goblet cells. This is characterized by a discontinuous single layer in the small intestine and a dual-layered structure in the colon, serving as the initial physical interface separating luminal microbes from the intestinal epithelium[23,24]. The epithelium is a monolayer of columnar cells interconnected by tight junctions, forming a selective permeability barrier[25]. Underlying this epithelial

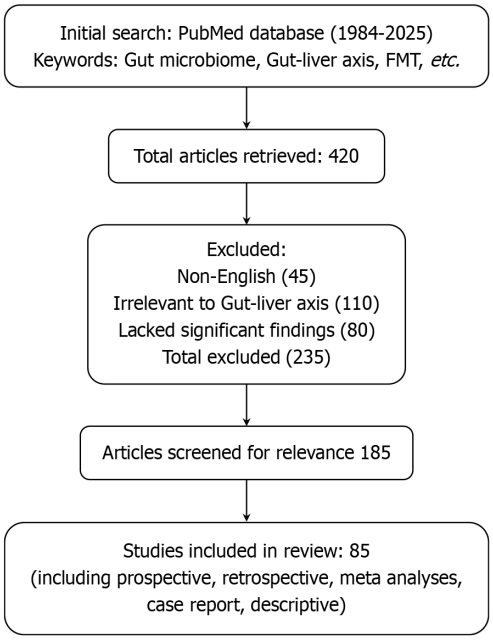
Initial search: PubMed database (1984-2025)
Keywords: Gut microbiome, Gut-liver axis, FMT, *etc.*
Total articles retrieved: 420
Excluded:
Non-English (45)
Irrelevant to Gut-liver axis (110)
Lacked significant findings (80)
Total excluded (235)
Articles screened for relevance 185
Studies included in review: 85
(including prospective, retrospective, meta analyses,
case report, descriptive)

Figure 2 Methodology. A flow diagram outlining the literature search and study selection process for this review. A total of 420 articles were retrieved from the PubMed database using keywords related to the gut microbiome and gut-liver axis. After screening, 85 studies were included in the final review. FMT: Fecal microbiota transplantation.

layer is an expansive network of mononuclear phagocytes, including intestinal macrophages and dendritic cells, which actively survey and phagocytose translocating microorganisms or luminal antigens. Moreover, distinct cell populations contribute to the functional specialization and regional regulation of the intestinal barrier in adults, particularly in relation to antigen uptake from the lumen. For example, within the epithelium that overlays gut-associated lymphoid tissue (GALT) such as Peyer's patches, specialized epithelial cells known as microfold (M) cells are responsible for translocating luminal antigens to the underlying antigen-presenting cell[26]. Glycosylphosphatidylinositol-anchored proteins, such as glycoprotein 2 and cellular prion protein, along with β1-integrin, aid in antigen translocation *via* M cells [26]. This process facilitates immune response initiation, including B lymphocyte activation and priming within the associated lymphoid tissue, which leads to antigen-specific immunoglobulin A secretion[27]. Lymphatic drainage from GALT to the mesenteric lymph nodes serve as an additional checkpoint to prevent microbial dissemination[23]. Apart from the physical and immunological barriers, microbial colonization is further restricted by acidic potential of hydrogen, digestive enzymes and bile acids in the proximal small intestine.

Another key regulatory mechanism within the gut-liver axis involves interactions between bile acids and the microbiota, which collectively impact metabolic processes, immune responses, and epithelial barrier integrity. Bile acids serve as endogenous signaling ligands that autoregulate their biosynthetic pathways and exert systemic metabolic effects by modulating lipoprotein, glucose, xenobiotic, and energy metabolism. These actions are primarily mediated through activation of nuclear receptors such as farnesoid X receptor (FXR) and membrane-bound receptors like the Takeda G protein-coupled bile acid receptor 5 (TGR5)[28]. Studies have shown that gut microbiota modulates key enzymes involved in bile acid synthesis, mainly *CYP7A1*, *CYP7B1*, and *CYP27A1*[29]. The gut microbiota also plays a pivotal role in shaping bile acid metabolism by catalyzing primary bile acid deconjugation, dehydroxylation, and dehydrogenation reactions within the distal small intestine and colon[30]. While the microbiota modifies bile acids, these metabolites shape microbial diversity and function. Bile acids modulate gut microbial ecology by selectively enriching bile-tolerant, metabolizing species and exerting inhibitory effects on bile-sensitive bacterial populations[29].

Bile acids are known not only for their ability to directly kill bacteria by disrupting their membranes, but also for their indirect role in modulating the immune system. By activating FXR, bile acids induce the expression of host-derived antimicrobial mediators, such as inducible nitric oxide synthase, and influence the production of both harmful and beneficial interleukins (ILs), thereby influencing gut microbial composition through immune signaling pathways[31]. Bile acids can stimulate the release of pro-inflammatory ILs, such as IL-1α and IL-1β, which drive inflammatory processes associated with diseases like inflammatory bowel disease and liver inflammation, a response that is amplified when dysbiosis alters bile acid metabolism, creating a cycle of inflammation and tissue damage[32]. Conversely, certain bile acids promote beneficial ILs like IL-18 and IL-22, which help maintain intestinal barrier integrity and prevent microbial translocation[33]. The gut microbiota-bile acid-IL-22 axis orchestrates protective immune responses, but dysbiosis-induced reductions in IL-22 compromise the epithelial barrier and perpetuate microbial imbalance[33]. Furthermore, TGR5 signaling by bile acids facilitates epithelial repair and regeneration, influencing intestinal barrier integrity[34]. Hence, studies in critically ill individuals suffering from cholestatic liver failure have shown that aberrant TGR5 activity is implicated in impairing innate immune responses[35,36].

A further important metabolic product of gut microbial activity are short-chain fatty acids (SCFAs), such as acetate, propionate and butyrate, derived from dietary carbohydrates, mucin and proteins[37,38]. Butyrate metabolism by colonocytes creates a hypoxic environment, which fosters the proliferation of obligate anaerobic bacteria while concurrently restricting pathogenic microbe colonization[39]. SCFAs play multifaceted roles in the gut-liver axis, including modulation of host metabolism through gut hormone secretion (glucagon-like peptide-1, peptide YY) and provision of energy substrates[40]. SCFAs also contribute to immune balance by regulating cytokine profiles and T cell responses, particularly regulatory T cells and Th17 cells[41,42].

A comprehensive understanding of these mechanisms is critical for identifying the underlying disruptions that contribute to the development and progression of diverse pathological conditions and guide targeted therapeutic strategies.

ROLE OF MICROBIOME IN LIVER DISEASES

Alcoholic liver disease

Alcohol consumption exerts direct and early effects on the gut microbiota, preceding hepatic fibrosis onset[43]. Jejunal aspirates from individuals with chronic alcohol use have consistently demonstrated intestinal overgrowth of both aerobic and anaerobic microbes[44]. Metagenomics profiling in alcohol-exposed individuals and murine models has revealed decreased microbial diversity, with a notable shift toward increased *Proteobacteria* and reduced levels of *Bacteroidetes, Firmicutes*, and *Lactobacillus spp*.[45-47]. Notably, in patients with severe alcoholic hepatitis, a distinct microbial signature characterized by elevated levels of *Bifidobacteria* and *Streptococci* has been identified[48]. Chronic alcohol consumption also alters nutrient availability for gut microbes, as alcohol administration has been shown to reduce the levels of both total and branched-chain amino acids within the intestinal environment[49].

Alcohol-induced gut dysbiosis enhances bile acid deconjugation in the intestine, thereby increasing hepatocyte exposure to more cytotoxic bile acids. This microbial imbalance interferes with the FXR-fibroblast growth factor 15 (FGF15) signaling pathway, which leads to the suppression of FXR activation in intestinal cells. Studies in mice show that modulating this axis through depletion of commensal bacteria with non-absorbable antibiotics or by restoring FXR-FGF15 signaling can ameliorate alcoholic liver disease (ALD)[50]. Chronic alcohol exposure also compromises intestinal epithelial barrier integrity. It induces low-grade intestinal inflammation, characterized by an increased abundance of tumor necrosis factor-alpha (TNF-α)-producing monocytes and macrophages, which activates myosin light-chain kinase, leading to the disruption of epithelial tight junction proteins. This breakdown in barrier integrity promotes intestinal permeability, facilitating the translocation of microbial products and contributing to hepatic inflammation[51].

Multiple studies have shown that prolonged alcohol intake elevates lipopolysaccharide (LPS) concentrations (from the gram-negative bacterial wall) in both the portal and systemic circulation[52,53]. A study demonstrated that acute alcohol binge in healthy individuals leads to a rapid rise in LPS and bacterial 16S rDNA serum levels, indicating compromised intestinal barrier integrity. Additionally, peptidoglycan, a structural component of gram-positive bacteria, was also identified in the circulation of individuals with chronic alcohol use[54]. Elevated levels of LPS reaching the liver exert several biological effects. Firstly, LPS promotes immune cell infiltration and activation, triggering the release of pro-inflammatory cytokines. Secondly, it alters hepatocyte function, contributing to the development of cholestasis[55]. Thirdly, both LPS and the resulting inflammatory mediators stimulate hepatocytes to produce acute-phase proteins, including serum amyloid A, LPS-binding protein, fibrinogen, C-reactive protein, IL-6, and ceruloplasmin[56].

Overall, the microbiome serves as a critical mediator between alcohol exposure and liver pathology through a complex interplay of metabolic, immunological, and barrier-related mechanisms. Continued exploration of the gut-liver axis has paved the way for novel microbiota-directed interventions in the treatment of ALD.

MASLD

MASLD, also known as non-alcoholic fatty liver disease, encompasses a spectrum of liver conditions ranging from benign hepatic steatosis to progressive non-alcoholic steatohepatitis (NASH), which may advance to fibrosis, cirrhosis, and eventually hepatocellular carcinoma. Evidence indicates that the gut microbiota contributes to MASLD pathogenesis[57,58]. SCFAs produced by gut bacteria have been implicated in the development of MASLD, largely due to their potential role in promoting obesity. Evidence for microbiota alterations in obesity was further strengthened when shotgun metagenomics sequencing revealed a microbiome profile linked to advanced fibrosis in MASLD patients, marked by elevated levels of *Escherichia coli* and *Bacteroides vulgatus*[59]. Likewise, an increased prevalence of the *Escherichia* genus has been reported in obese pediatric patients diagnosed with NASH[60].

The shift in gut microbial composition due to high-fat diet compromises both the intestinal epithelial barrier and the gut-vascular barrier[61]. This was also seen when mice subjected to high-fat or fiber-deficient diets exhibited alterations in colonic microbiota composition, leading to enhanced bacterial translocation, thinning of the protective mucus layer, disruption of tight junction protein localization within the intestinal epithelium, and the development of low-grade intestinal inflammation[62-64]. In this context, subclinical inflammation is marked by a decline in regulatory T cell populations, along with elevated levels of interferon-γ-secreting Th1 and cluster of differentiation (CD) 8^+ T cells, as well as an increase in IL-17-producing γδ T cells within the lamina propria[63]. Disrupted bile acid signaling is another consequence of intestinal microbiota alterations observed in both high-fiber-fed mice and individuals with MASLD. In these cases, the gut microbiome is enriched with bacterial species capable of generating secondary bile acids, such as deoxycholic acid, which acts as an FXR antagonist, thereby inhibiting FXR and fibroblast growth factor receptor 4-dependent signaling pathways[65].

Although several bacterial species have been implicated in MASLD progression, few strains have been investigated for their potential therapeutic benefits, *Akkermansia muciniphila* (*A. muciniphila*) being a prominent one. Administration of *A. muciniphila* confers protection against various metabolic disturbances, including increased adiposity, metabolic endotoxemia, inflammation in adipose tissue, and insulin resistance[66-68]. Moreover, multiple studies have highlighted its effectiveness in preventing the progression of obesity and related metabolic disorders[66,68,69]. In addition, both direct supplementation with *A. muciniphila* and strategies aimed at enhancing its abundance in the gut, through dietary modifications or pharmacological interventions, have shown promising results in ameliorating MASLD *in vivo*[70].

PBC

PBC pathogenesis arises from the complex interplay of genetic-immune dysfunction and environmental factors amplified by gut dysbiosis, which disrupts bile acid homeostasis and promotes inflammation[71]. In PBC, loss of immune tolerance triggers autoreactive $CD4^+$ and $CD8^+$ T cells and the production of antimitochondrial antibodies against the E2 subunit of pyruvate dehydrogenase complex antigen on biliary epithelial cells, leading to chronic bile duct inflammation[72]. This is compounded by impaired biliary protection due to downregulation of the anion exchanger 2, which weakens the bicarbonate barrier and increases cholangiocyte susceptibility to bile acid-induced apoptosis[72]. Additionally, immune dysregulation characterized by dominant Th1 and Th17 responses and dysfunctional regulatory T cells sustains chronic inflammation and promotes fibrosis[72].

The gut microbiome further modulates disease progression, as patients with PBC exhibit microbial dysbiosis with reduced diversity, enrichment of pathobionts such as *Veillonella* and *Klebsiella*, and depletion of beneficial genera like *Faecalibacterium*, disrupting gut barrier integrity and promoting bacterial translocation and hepatic immune activation[71,73]. Altered bile acid metabolism, marked by excessive conversion of primary to toxic secondary bile acids (*e.g.*, deoxycholic acid) and impaired microbial detoxification, exacerbates cholangiocyte injury and cholestasis[20,71]. Mendelian randomization studies support causal links between microbiota and PBC risk, identifying risk-enhancing taxa (*Coriobacteriia*, *Coriobacteriales*, *Selenomonadales*, *Bifidobacteriales*, *Lachnospiraceae_UCG_004*) and protective taxa (*Deltaproteobacteria*, *Peptostreptococcaceae*, *Ruminococcaceae*)[20,74].

PSC

PSC pathogenesis involves complex interactions between genetic predisposition, immune dysregulation, and environmental factors, with the gut microbiome playing a pivotal role *via* the gut-liver axis. PSC is driven by a combination of genetic susceptibility such as human leukocyte antigen (HLA) (HLA B8, HLA DR3, HLA DR6) and non-HLA genes *e.g.*, *FUT2,* which is involved in handling translocated bacteria that influence microbial diversity, bile acid metabolism and immune dysregulation[6,75,76]. Rupp *et al*[7] concluded that the *FUT2* genotype in patients with PSC is associated with increased risk of fungobilia, cholangitis and dominant stenosis[7].

PSC shows a strong association with inflammatory bowel disease, particularly ulcerative colitis, highlighting the pivotal role of the gut-liver axis in its pathogenesis. This concept was first proposed by Lichtman *et al*[77] in 1990. A key mechanism underlying PSC pathogenesis involves the translocation of gut-derived bacteria and their by-products, including pathogen-associated molecular patterns, across a compromised intestinal barrier. These microbial components enter the liver *via* portal circulation and activate hepatic innate immune responses, particularly through Kupffer cells and hepatic stellate cells. This leads to the release of pro-inflammatory cytokines such as TNF-α and IL-1β, along with T lymphocyte recruitment. Concurrently, overexpression of adhesion molecules on biliary epithelial cells facilitates cholangiocyte targeting, driving localized inflammation and ultimately contributing to progressive biliary fibrosis[75,78].

Similar to PBC, microbial dysbiosis in PSC is characterized by enrichment of pathobionts (*e.g.*, *Veillonella*, *Enterococcus*, *Ruminococcus*, *Clostridium, etc.*), and loss of beneficial taxa (*e.g.*, *Faecalibacterium*, *Coprococcus*) which leads to a compromised gut barrier allowing for microbial translocation and subsequent hepatic immune activation[75]. Low levels of *Bacteroides thetaiotaomicron* and *Faecalibacterium prausnitzii* results in decreased SCFA production, curtailing their anti-inflammatory effects. Furthermore, abundance of *Enterococcus faecalis* results in gelatinase production, disrupting intestinal barrier, exacerbating leaky gut syndrome, and resulting in cholangiocyte injury and cholestasis[5]. Notably, *Klebsiella pneumoniae* forms pores in the intestinal wall, allowing other pathogens to enter portal circulation and activate Th17-driven hepatobiliary inflammation in murine models, effects that are reversible with targeted antibiotics[79]. Similarly, patients with PSC also show increased fungal biodiversity and enrichment of pathogenic genera like *Exophiala,* which facilitates bacterial translocation in the gut by disrupting intestinal integrity, alongside depletion of beneficial flora like *Saccharomyces cerevisiae,* which has anti-inflammatory effects, hence enhancing bacteria-fungi crosstalk[80].

HE

Recently, gut microbiota dysbiosis has been identified as a significant factor in HE pathophysiology, contributing to hyperammonemia, systemic inflammation, neuroinflammation, and endotoxemia in patients with cirrhosis. SIBO represents a pathological imbalance in the microbial composition of the small intestine. It is reported in approximately 48% to 73% of patients with liver cirrhosis. The development of SIBO is attributed to impaired intestinal immunity, delayed gastrointestinal motility, and reduced bile acid secretion. SIBO has been closely associated with the severity of advanced liver disease and is now recognized as a significant risk factor for HE. In individuals with HE, SIBO contributes to gut dysbiosis characterized by diminished populations of beneficial commensals, reduced microbial diversity, and overgrowth of pathogenic gram-negative bacteria[81].

The symbiotic interaction between the gut microbiota and human host plays a key role in protein, lipid and carbohydrate metabolism. The host supplies essential nutrients that support microbial growth, while the gut microbiota performs vital metabolic functions that benefit the host. For instance, gut bacteria ferment indigestible dietary fibers into

SCFAs, which are a crucial energy source for colon epithelial cells. SCFAs also help strengthen the intestinal barrier by promoting the production of tight junction proteins and mucin. In liver cirrhosis and HE, this delicate metabolic balance is disrupted. Important SCFA-producing bacteria, such as *Anaerostipes caccae, Bacteroides eggerthii*, and certain *Clostridium* species, are reduced in patients with HE, resulting in lower SCFA levels. This reduction compromises the gut barrier, resulting in increased intestinal permeability.

Additionally, bile acid levels and bile acid metabolism by gut bacteria are diminished in cirrhosis. Intestinal immune function is impaired, further compromising the gut's ability to maintain a healthy barrier. These changes allow harmful substances, including neurotoxins, to more easily pass into the bloodstream. One of the major toxins implicated in HE is ammonia. In cirrhosis, impaired liver function and portosystemic shunting reduce the liver's ability to detoxify ammonia. This leads to elevated blood ammonia levels, with further contributions from the kidneys and muscles. Ammonia can cross the blood-brain barrier and enter astrocytes (support cells in the brain), where it is converted to glutamine. Excess glutamine causes the astrocytes to swell, leading to oxidative stress, cellular dysfunction, and ultimately, neurological impairment. Emerging research also shows that certain gut bacteria, such as *Streptococcus salivarius*, are more abundant in patients with HE and may contribute to increased ammonia production. In addition, altered bile acid signaling and neuroinflammation further affect brain function by increasing blood-brain barrier permeability. Together, these mechanisms explain how disruptions in gut microbiota and metabolism contribute to the development and progression of HE[82].

THERAPEUTIC STRATEGIES

FMT

FMT is gaining popularity as a method to alter gut microbiota in various diseases (Figure 3). It involves transferring stool-derived gut microbes from a healthy donor into the gastrointestinal tract of a patient. This therapy is mainly used to treat gastrointestinal conditions caused by harmful or opportunistic microorganisms. However, recent studies suggest that FMT also holds promise in managing liver diseases. FMT can be delivered through different routes: Orally *via* capsules or upper gastrointestinal access; Nasally through a nasogastric tube; and rectally using colonoscopy or enema. Among these, rectal administration through colonoscopy is generally considered the most effective method. On the other hand, upper gastrointestinal methods, such as using a nasogastric tube or endoscopy, expose the entire gastrointestinal tract to donor stool and may increase the risk of complications, especially in the lungs and upper gastrointestinal tract due to potential pathogens. Encouragingly, the use of oral FMT capsules has also been explored. In a randomized controlled trial involving 22 obese patients, FMT capsules were found to be safe and effective. They led to a favorable shift in gut microbiota and a reduction in taurocholic acid levels, metabolites that can harm the liver and disrupt bile acid metabolism[3,83,84].

Studies involving transplantation of fecal microbiota from PBC patients into pseudo-germ-free mice have shown increased serum ALP levels, total bile acids, liver injury and increased serum glycylproline dipeptidyl aminopeptidase level, highlighting the role of altered gut microbiota in disease progression and suggesting that correcting dysbiosis could be beneficial for treatment[85]. Although direct clinical trials of FMT in PBC are limited, improving gut microbial composition is considered a promising strategy to restore bile acid homeostasis and reduce immune-mediated bile duct damage[71]. In PSC, FMT has been evaluated more extensively. A pilot clinical trial conducted in 2019 demonstrated that FMT is safe in patients with PSC who have concurrent inflammatory bowel disease, with increased bacterial diversity and engraftment correlating with ≥ 50% reductions in ALP levels in about 30% of participants by week 24, indicating potential biochemical improvement[86]. FMT in PSC is in a phase IIa, partially blinded randomized controlled trial designed to assess the efficacy and safety of repeated FMT in patients with non-cirrhotic PSC and concomitant inflammatory bowel disease. The primary end point of the trial is decreased ALP levels over 48 weeks. The trial also incorporates comprehensive translational analyses to explore gut-liver axis pathways through metagenomics, metatranscriptomics, metabolomics, and immunological profiling[15]. The rationale is that FMT can restore beneficial taxa depleted in PSC (*e.g.*, *Faecalibacterium*), reduce pathobionts (*e.g.*, *Veillonella*, *Enterococcus*), and hence improve the gut barrier integrity, decreasing bacterial translocation and hepatic immune activation[15].

Moreover, emerging experimental and clinical evidence also supports the therapeutic potential of FMT in ALD. In murine models, fecal transfer from alcohol-resistant donor mice into alcohol-sensitive recipients prevented steatosis and liver inflammation, restoring gut microbial homeostasis[87]. Early human trials in severe alcoholic hepatitis patients who were ineligible for corticosteroid therapy demonstrated a reduction in *Proteobacteria,* enrichment of *Firmicutes*, and higher 1-year survival rates in those receiving nasojejunal FMT compared to patients who did not receive stool transfer (87% *vs* 33%)[88]. Furthermore, Philips *et al*[89] showed better long term outcomes of FMT *vs* standard care (SoC) in ALD patients, with significantly lesser ascites (34.3% *vs* 73.1%, $P = 0.003$), critical infections (17.1% *vs* 53.8%, $P = 0.003$), and alcohol relapse (28.6% *vs* 53.8%, $P = 0.04$). It also reported higher 3-year survival in the FMT group than in the SoC group (65.7% *vs* 38.5%, $P = 0.052$). Preclinical and early clinical data suggest that FMT may restore gut microbiota, strengthen barrier function, reduce inflammation, and improve survival in ALD, though larger trials are needed to confirm its efficacy.

Prebiotics and probiotics

Prebiotics are non-absorbable substances, usually certain carbohydrates that support the growth of healthy gut bacteria. When fermented by gut microbes, they increase beneficial bacteria, produce SCFAs, lower the potential of hydrogen in the intestines, and make the environment less favorable for harmful bacteria. One common prebiotic, lactulose, has

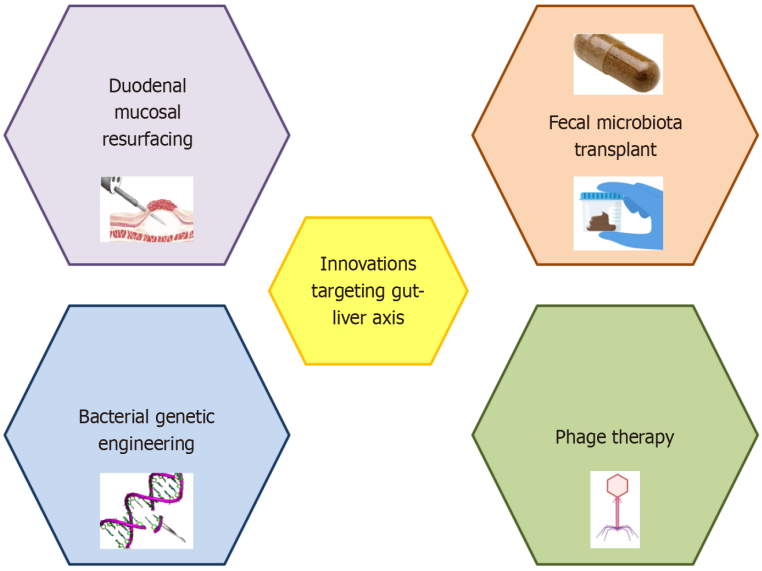

Figure 3 Therapeutic strategies targeting the gut-liver axis. A selection of innovative therapies designed to modulate the gut-liver axis.

proven effective in treating HE. A Cochrane review of 38 clinical trials showed that non-absorbable disaccharides like lactulose significantly improve HE[90]. Another analysis found that amongst lactulose, rifaximin, probiotics, and L-ornithine L-aspartate, lactulose was the only treatment shown to reverse minimal HE, prevent progression to overt HE, and improve quality of life[91]. Moreover, early studies showed that lactulose also increases beneficial bacteria like *Lactobacillus* and *Bifidobacteria*[91].

Probiotics are live microorganisms that regulate the immune system by modulating gut microbiota, improving bile acid metabolism, and reducing immune-mediated damage. Probiotics have also been studied in HE treatment from yogurts to capsules. Probiotics may help by strengthening the gut barrier and reduce portal hypertension[82].

In PBC, probiotics such as *Lactobacillus plantarum* Lp2 demonstrate hepatoprotective effects in murine models by inhibiting LPS-induced inflammation and oxidative stress, while strains like *Lactobacillus rhamnosus* GG enhance bile acid excretion *via* bile salt hydrolase activity and reduce bile acid synthesis through upregulation of the intestinal FXR-FGF15 signaling pathway, potentially mitigating cholestatic injury[92,93]. There is no validated study to suggest the role of prebiotics and symbiotics in PBC and PSC[94]. For PSC, a randomized placebo-controlled cross-over pilot study recruited 14 patients with concomitant inflammatory bowel disease. Patients were randomized to treatment with 3 months of probiotic blend, which included *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus salivarius*, *Lactococcus lactis*, *Bifidobacterium bifidum* and *Bifidobacterium*. Results showed no significant improvement in symptoms, liver biochemistry, or fibrosis markers with probiotics, highlighting inconsistent clinical outcomes[95]. However, combined therapy with steroids, probiotic and salazosulfapyridine in patients with concomitant inflammatory bowel disease and PSC improved liver fibrosis from 10.5% to 3.6% in a case report[96]. Despite promising preclinical data, rigorous human studies are needed to validate efficacy, particularly in PBC where clinical evidence is scarce[71].

Antibiotics and antifungals

Antibiotics and antifungals help restore microbial balance by reducing pathogenic bacteria and fungi that contribute to intestinal barrier dysfunction and hepatic inflammation, thus playing a pivotal role in modulating gut-liver axis. Shah *et al*[97] concluded that in patients with PSC, antibiotics like metronidazole, minocycline, rifaximin and vancomycin significantly improved serum ALP, bilirubin, and Mayo risk score with vancomycin achieving greatest reduction in ALP levels ($P < 0.002$)[97]. Possible mechanisms explaining the high efficacy of vancomycin include selective targeting of Gram-positive bacteria, including *Clostridium* species, which convert primary bile acids to toxic secondary bile acids, hence reducing the harmful bile acid levels[97]. Moreover, vancomycin alters gut microbiota by reducing pathogenic bacteria like *Bacteroidia* and exerts immunomodulatory effects by reducing proinflammatory cytokines and increasing regulatory T cells and transforming growth factor β[98,99]. However, broad-spectrum antibiotics risk disrupting beneficial microbiota and may exacerbate toxicity[100].

Furthermore, rifaximin is an oral antibiotic used in the management of diarrhea caused by *Escherichia coli*, and it is useful in the management of HE. It works by altering the gut microbiota and is effective in treating both covert and overt HE. In patients with cirrhosis and minimal HE, rifaximin's effects on the metabiome, including brain function, liver disease severity, gut bacteria, and metabolism, were studied. Only small changes were seen in the types of gut bacteria after treatment, with a slight decrease in *Veillonellaceae* and an increase in *Eubacteriaceae*. However, patients experienced noticeable improvements in mental function, reduced endotoxin levels, and an increase in healthy long-chain fatty acids in their blood. Interestingly, rifaximin appeared to shift the relationship between harmful bacteria and toxic substances like ammonia and oxidative stress. Before treatment, these bacteria were positively linked to harmful metabolites, but after rifaximin therapy, this relationship became negative. This suggests that rifaximin may improve brain function by changing how gut bacteria behave metabolically, rather than simply changing which bacteria are present[12,101].

Similarly, antifungals like fluconazole can counter opportunistic fungal overgrowth (*e.g.*, *Exophiala*), which disrupts gut-barrier integrity and facilitates bacterial translocation and can be used in patients who have confirmed fungal infection, which may serve as an adjunctive measure in PSC management[102].

Phage therapy

Phage therapy is an emerging treatment that uses viruses called bacteriophages, or phages, to target and kill harmful bacteria in the body. These phages are viruses that infect only bacteria, not human cells. When introduced into a patient, they seek out and destroy the specific bacteria causing an infection. Historically, phage therapy has been used to treat infections caused by bacteria such as *Staphylococcus*, *Streptococcus*, *Vibrio*, *Klebsiella*, *Enterobacter*, *Shigella*, *Escherichia*, *Pseudomonas*, and *Providencia*. One major advantage of phages over antibiotics is their ability to target only specific bacterial species or strains, while also multiplying and continuing to attack other harmful bacteria. Interestingly, phage therapy can also influence the gut microbiota. In two randomized controlled trials, phage treatment improved gut microbiome composition, helped regulate metabolism, and reduced gastrointestinal symptoms by targeting specific bacterial groups. Because certain gut bacteria play a role in the development of liver diseases, phage therapy holds promise as a potential treatment by eliminating those harmful bacteria involved in liver disease progression[3,103,104].

Genetic engineering

A new approach to treating hyperammonemia involves modifying gut bacteria through genetic engineering. Using gene editing technology, bacteria can be programmed to produce certain enzymes by inserting specific genes. These engineered bacteria can be delivered to the body usually by mouth, where they travel to the gut and settle there. Once in the gut, these special bacteria help convert harmful substances into inert ones[105,106]. Kurtz *et al*[11] developed a modified bacterium called SYNB1020. When taken orally, this bacterium can live in the gut and turn ammonia into L-arginine, a non-toxic compound. This helps lower the level of ammonia in the blood and may benefit patients with liver-related conditions.

Duodenal mucosal resurfacing

Duodenal mucosal resurfacing is a new minimally invasive procedure aided by an endoscope. During this procedure, a catheter with a balloon is inserted into the duodenum. The balloon is inflated to create sections within the duodenum. Then, saline is injected under the mucosal lining of the bowel to gently lift it, and this lining is treated with mucosal ablation, using hot and cold water to remove the old mucosa. This treatment is performed along a specific part of the duodenum, from just below the main papilla to the ligament of Treitz. After the mucosa is removed, new, healthy cells grow back. This regeneration helps restore normal gut function and supports a healthier gut environment by rebalancing hormones and signals from the intestine[107,108].

Recent precision medicine approaches, which include bile acid modulators and immune pathway inhibitors tailored to patients' microbial and genetic profiles, are summarized in Table 1[2,7,9,10,109-112].

Table 1 Personalized therapies targeting microbial and genetic profiles

Innovation/strategy	Description	Example	Ref.
FUT2 genotype-based interventions	Personalized treatment based on *FUT2* secretor status to prevent fungal dysbiosis and strictures	Early antifungal treatment in *FUT2* non-secretors with PSC	Rupp *et al*[7]
Bacteriophage therapy	Use of genetically modified bacteria or bacteriophages to restore healthy microbiota and reduce pathogens	Targeting *Klebsiella pneumoniae* and *Enterococcus* in PSC to reduce Th17-driven inflammation	Ichikawa *et al*[9]
Inflammasome inhibitors	Suppress cholangiocyte inflammasome activation and IL-1β release	OLT1177 in experimental models	Yao *et al*[10]
Genomic profiling and targeted therapy	Tailoring treatment based on tumor or patient genetic mutations	FGFR2-selective tyrosine kinase inhibitors for advanced cholangiocarcinoma harboring an FGFR2 gene fusion or rearrangement, and an IDH1 inhibitor for IDH1-mutated cholangiocarcinoma	Khosla *et al*[109]
Bile acid receptor agonists	Modulate bile acid synthesis and secretion to reduce cholestasis and liver injury	Intercept INT-767 (dual FXR/TGR5 receptor agonist) maralixibat (selective ileal bile acid transporter inhibitor)	Baghdasaryan *et al*[2]; Bowlus *et al*[110]
Peroxisome proliferator activated receptor (PPAR) α/δ agonists	Reduce bile acid synthesis, inflammation, and fibrosis	Elafibranor (dual PPARα/δ agonist) and seladelpar (PPAR δ agonist) are FDA approved. Saroglitazar (dual PPARα/γ agonist) in clinical trials	Saeedian *et al* [111]
Multi-omics integration	Integration of genomics, metabolomics, and microbiomics to stratify patients and optimize therapy	Potential of multi-omics-based classification to inform prognosis and guide pre- and postoperative therapeutic decisions	Alaimo *et al*[112]

PPAR: Peroxisome proliferator activated receptor; FGFR2: Fibroblast growth factor receptor 2; IDH1: Isocitrate dehydrogenase 1; IL: Interleukin; PSC:

Primary sclerosing cholangitis; FXR: Farnesoid X receptor; TGR5: Takeda G protein-coupled bile acid receptor 5; FDA: Food and Drug Administration.

CONCLUSION

Microbiome-based therapies are revolutionizing the management of liver diseases by shifting toward personalized, precision medicine approaches. By restoring microbial homeostasis, enhancing barrier integrity, and personalizing interventions based on genetic and microbial signatures, clinicians can more effectively halt disease progression and improve patient outcomes. Although promising challenges remain in optimizing treatment regimens, ensuring safety, and refining patient selection. Continued research into the gut-liver axis and the integration of advanced diagnostics and therapeutics promise a new era of individualized and disease-modifying care for patients with liver diseases.

FOOTNOTES

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